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Remarks

Claims 1-21, 23-28, 30-44, and 68-71 are currently pending.

As a preliminary matter, applicant acknowledges that the response filed July 15, 2003 was sufficient to overcome the previous rejections under 35 U.S.C. §§ 102 and 103. However, in the September 30, 2003 Office Action, claims 1-17, 25, 26, 30-34, 36-44, 68, and 69 have been rejected under 35 U.S.C. § 103, claims 70-71 remain allowed, and claims 27 and 28 would be allowable if rewritten in independent form.

Applicant addresses the rejections herein, and in view of these remarks, applicant requests reconsideration of the rejections.

Rejection Under 35 U.S.C. § 103

Claims 1-17, 25, 26, 30-34, 36-44, 68, and 69 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Weinshank et al. (U.S. Pat. No. 5,595,880) in view of Dolly et al. (WO 95/32738). In particular, the Examiner states that it would have been obvious to "apply the conjugate of Dolly et al. for the method of screening drugs of the method of Weinshank et al." (Office Action, page 3).

Applicant traverses the rejection.

Applicant submits that the combination of applying the conjugate of Dolly et al. for the method of screening drugs does not make the presently claimed invention obvious.

The present claims are generally directed to an agent comprising a therapeutic component and a targeting ligand coupled to the therapeutic component, or a method of making such an agent. The targeting ligand is effective to bind to the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s).

Applicant respectfully submits that neither Weinshank et al. nor Dolly et al. discloses, teaches, or even suggests the present invention. Certainly, the combination of a conjugate and a screening method do not suggest the present invention. Accordingly, applicant submits that the current rejection under 35 U.S.C. § 103 cannot be properly maintained.

Applicant submits that one of ordinary skill in the art would not be motivated to combine the teachings of Dolly et al. with the teachings of Weinshank et al. Moreover, even if the teachings of Dolly et al. and Weinshank et al. were to be erroneously combined, the combination would not disclose, teach, or suggest the present invention.

For example, Dolly et al. discloses a conjugate which includes an inactive Clostridial neurotoxin component that is used to target cells that have neurotoxin receptors, for example, neurons innervating muscles. In contrast, Weinshank et al. discloses cells that express the alpha-2B adrenergic receptors. Adrenergic receptors are not neurotoxin receptors. Based on the disclosure of Dolly et al., applicant submits that a person of ordinary skill in the art would conclude that the conjugates of Dolly et al. do not target and bind to the cells that express the alpha-2B adrenergic receptors of Weinshank et

al. because there is no indication whatsoever that such cells of Weinshank et al. have neurotoxin receptors. Thus, applicant submits that a person of ordinary skill in the art at the time of the invention would not be motivated to combine the two references since the references are directed to agents that are related to distinct and different cellular systems, e.g., cells that have neurotoxin receptors as opposed to cells that express the alpha-2B adrenergic receptors.

To the extent the Examiner maintains the rejection, applicant requests the Examiner to specifically point out where in the references a motivation or suggestion is provided to obtain the claimed agents and methods for making such agents. As the Federal Circuit has clearly indicated, "[a]lthough a reference need not expressly teach that the disclosure contained therein should be combined with another, the showing of combinability, in whatever form, must nevertheless be clear and particular." (*In re Dembiscak*, 175 F.3d 994, 999 (CAFC) 1999) emphasis ours). Absent such a showing, applicant requests that the rejections be withdrawn.

Nevertheless, even if the references could be combined, which applicant does not concede, applicant submits that the combination of references fails to disclose, teach, or even suggest all of the limitations recited in the present claims.

For example, Dolly et al. discloses an agent having a targeting component that binds to toxin receptors, not alpha-2B or alpha-2B/alpha-2C receptor subtypes. Weinshank et al. does not disclose, teach, or even suggest any agent that comprises a targeting component coupled to a therapeutic component. Thus,

applicant submits that the combination of references does not disclose, teach, or even suggest an agent comprising a therapeutic component and a targeting ligand effective to bind to an alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype, as recited in the present claims.

In addition, using the conjugate of Dolly et al. to deliver chemical compounds to the cytosol of neuronal cells, as suggested by the Examiner, would not be successful since it cannot be determined that the cells disclosed by Weinshank et al. disclose receptors for the toxins. Instead, the cells disclosed by Weinshank et al. express the alpha-2B adrenergic receptors. Weinshank et al. fails to disclose, teach, or even suggest that these adrenergic cells have any receptor-like mechanism for the targeting component of Dolly et al., i.e., the inactivated toxin conjugates. Clostridial neurotoxins bind to neurotoxin receptors, or neurotoxin receptor-like elements. Clostridial neurotoxins do not bind to adrenergic receptors. Thus, contrary to the Examiner's contention, applicant submits that a person of ordinary skill in the art would conclude that the conjugates of Dolly et al., which use a neurotoxin as a targeting component, do not recognize or bind to receptors on the adrenergic cells disclosed by Weinshank et al. Without such a recognition or binding, the chemical compound of the conjugate could not be delivered to the cytosol of the cell. Thus, the combination of Weinshank et al. and Dolly et al. would be unsuccessful in achieving the intended result proposed by the Examiner.

In view of the above, applicant submits that the present claims, and claims 1-17, 25, 26, 30-34, 36-44, 68, and 69 in

particular, are unobvious from and patentable over the combination of Weinshank et al. in view of Dolly et al. under 35 U.S.C. § 103.

In addition, each of the present dependent claims is separately patentable over the prior art. For example, none of the prior art disclose, teach, or even suggest the present agents and methods for making the agents including the additional feature or features recited in any of the present dependent claims. Therefore, applicant submits that each of the present claims is separately patentable over the prior art.

In conclusion, applicant has shown that the present claims are unobvious from and patentable over the prior art under 35 U.S.C. § 103. Therefore, applicant submits that the present claims, that is claims 1-21, 23-28, 30-44, and 68-71 are allowable. Therefore, applicant requests the Examiner to pass the above-identified application to issuance at an early date. Should any matters remain unresolved, the Examiner is requested to call (collect) applicant's attorney at the telephone number given below.

Date: DEC. 30, 2003

Respectfully submitted,

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